The Pharmacological Treatment of Headache

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• **Often in the treatment of chronic headache, both physical and emotional factors are entailed. Therefore, the results of therapy are limited by the potentialities of the patient in therapy, the pharmacologic actions of the medications used, and the physician's interest and orientation toward the problem. The treatment of choice is generally a combination of psychotherapy and drug therapy. Results in a large series of tests with these types of headaches indicate the effectiveness of treatment is greatly influenced by the patient's psychological reaction to the treatment situation in general and in particular to having received a remedy from the physician. Patients with migraine did not respond to placebos as well as did patients with tension headache, post-traumatic headache and headache associated with hypertension.**

HEADACHE IS A SYMPTOM which may be associated with a variety of clinical conditions whether the underlying disorder be organic, psychologic or psychophysiologic. The appraisal of the results of any method of therapy in patients with chronic headache is extremely difficult, for the major criterion of effect, relief of pain, is subject to many variable factors.

Furthermore, a symptom related to the head is frequently associated with profound anxiety which is due not only to the underlying emotional conflicts responsible for the headache but the threat of the symptom itself. For headache may represent many things to the patient, among which are fear of loss of mind, of disorder of the brain or of impairment of intellectual capacity.

Reading the literature on treatment of chronic headache, a physician is confronted with reports of a consistently high degree of therapeutic success obtained with a variety of remedies. The success of each of the numerous remedies is attributed to the fact that it corrects some hypothecated defect. Among these are reports by certain allergists that over 80 per cent of the patients treated are cured or considerably improved. Ophthalmologists have stated that correction of refractive errors has resulted in considerable improvement in 90 per cent of the patients; endocrinologists note excellent results with various treatments; and reports from orthopedists have indicated successful management of migraine by the use of cervical traction in 85 per cent of cases. Certain psychoanalysts report successful therapy in all cases. Reports by internists claim almost equal success with thiamine chloride, calcium, potassium, histamine desensitization, use of antihistamine, sympatholytics, drugs, sedation, etc. The good results obtained by the primary investigators can seldom be duplicated by others.

With such a diversity of opinions and reports in therapy by the various disciplines, evaluation of pharmacotherapy becomes even more complicated. It is obvious that relative alleviation of symptoms is difficult to ascertain, not only from patient to patient, but also in the same patient during different periods of observation. These differences are emphasized by reports in the literature which, in some cases, show similar medication yielding completely opposite results, while in others the first glowing therapeutic success diminished to a feeble flicker in later studies.

In the majority of headache problems, the most effective treatment is to relieve the underlying cause. While the use of drugs, in some cases, may not solve the basic therapeutic problem, the importance of drugs in the treatment of headache cannot be minimized. In pharmacologic treatment, attempt is made to do one or more of the following: (1) Raise the pain threshold, (2) interrupt the mechanism producing pain, (3) reduce the emotional tension and anxiety associated with the pain.

In pharmacotherapy the efficiency of any drug does not depend upon its pharmacologic action alone.[3] Dosage, timing, mode of administration, tolerance, influence of pathological states, cumulative action and individual idiosyncrasy of the patient are factors of great importance. Furthermore, the efficiency depends greatly upon the patient-physician relationship, which includes, among other things, the attitude of the physician toward the medicine given (positive or negative) and the length and frequency of interviews with the patient. The author believes that patients' reactions to drugs not only depend upon the drug's effect on the underlying disorder responsible for the headache, but also upon the degree of incapacity, constitutional makeup of the patient, duration of symptoms, age of individual, and psychological setting of the therapeutic regimen

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and status of the patient. What the taking of medication symbolizes to the patient is also a contributory factor in treatment. Is the taking of medication a sign to the patient of weakness, of receiving omnipotent mystical power, punishment or aggression, love and affection? All these factors must be given serious consideration in the clinical usage of drugs in the treatment of headache.

The number and mass of therapeutic agents recommended for relief of headache indicates that there is no one specific form of therapy. Poor results with an agent which has been reported to be effective may indicate that the drug itself is unsatisfactory or that it is being improperly used. From the author's observations, it would appear that the most common causes of therapeutic failures are incorrect diagnosis, inappropriate, inadequate or improper administration of medication, inflexibility of therapeutic regimen and variables in the patient's emotional life.

METHOD

The author knows of no completely accurate method of clinical testing of drugs for headache therapy. The best method of drug evaluation would seem to be the use of the double blind technique in which all agents tested are employed in all subjects. Whenever possible, all "placebo-fast"* patients should be eliminated from the study. In all cases attempt should be made to test more than two agents, which minimizes the chance of placebo detection. Without these techniques, a study of hundreds of cases over a number of years is likely to yield inaccurate results. The trained observer has not proven as valuable a subject as the untrained.[1] The highly trained observer tends to be biased, having an interest in the outcome, whether scientific, pecuniary or emotional. Of course, learning can occur with any subject, but the results are more weighted with the experienced group.

Concurrent observations of the life situations and emotional reactions of the patient and, when possible, of the physician, are most important for critical appraisal of the specific value of the drug being investigated.

Appraisal of Drugs in Specific Headache Entities

The present discussion will be limited to some of the author's past studies on headaches associated primarily with an emotional disturbance (tension headache), cranial trauma (post-traumatic headache), migraine and hypertension.

Since the effectiveness of the various medicaments was said to vary in these specific groups, it is important to define the diagnostic categories used.

*It is normal to respond to placebo effects at times. Patients who almost always or almost never undergo placebo responses have personality patterns which depart from what may be considered the norm.

Differential Diagnosis

1. TENSION HEADACHE:

(a) *Clinical features.* Tension headache occurs in relation to constant or periodic emotional conflict, of which the patients are usually partially aware.[4] They have no prodromata, are usually bilateral, occipital or frontal, and may be accompanied by a variety of associated signs, including anxiety and nausea. Frequency and duration are variable.

(b) *Mechanisms.* The mechanism by which cranial structures give rise to headache in patients with psychic distress may operate at two levels, each applicable to a different group of psychogenic headaches.

In one group (tension headache) the mental conflict may stimulate the sympathetic or autonomic nervous system with change in the caliber of blood vessels or stimulation of the somatic motor system with contraction of skeletal muscles, particularly those of the neck.

In another group (conversion headache) the symptom represents a specific unconscious symbolic meaning, and conversion mechanisms are prevalent. Headache of this type cannot be distinguished from tension headache by clinical description alone.

In tension headaches muscular or vascular mechanisms may act independently or concomitantly. With muscle tension, sustained contraction of the skeletal muscles of the head and neck causes pain or dysesthesia in the neck and scalp. Associated with these muscular spasms may be ischemia which could be a contributory or primary factor in the induction of pain. It has also been hypothecated that excessive concentration of potassium in muscle from ischemia or sustained contraction stimulates the chemoreceptors in the tissues. Another factor responsible for the head pain may be a central spread of the excitatory effect of noxious stimulation of the soft tissues of the neck. This spread of pain is carried by the upper cervical nerves and may produce painful sensations in the forehead and face.

2. POST-TRAUMATIC HEADACHE:

One of the most frequent sequelae to injury of the head is post-traumatic headache. This occurs in approximately 60 per cent of patients who have had head injuries.[2] Post-traumatic headache resembles tension headache. The headache is usually referred to the side or part of the head which the patient associates with the injury. The physiologic mechanisms which are presumably involved in the production of post-traumatic headaches are distention of cranial blood vessels, sustained contraction of the skeletal muscles of the head and neck, and scarring of the extracranial soft tissues.

The incidence of prolonged headache in patients following head injury was associated with neurotic symptoms prior to injury, with symptoms of marked immediate emotional reaction to the injury, and with complicating environmental factors which might be presumed to cause the usual emotional stress.

3. MIGRAINE:

(a) *Clinical features.* Migraine may be defined as that form of headache which is characteristically paroxysmal, periodic, unilateral and throbbing. The headache occurs against a background of relative well-being, is often preceded by visual or psychological disturbances, and is usually associated with vomiting and irritability.

(b) *Physiological mechanisms.* The following physiological changes occur in an attack of migraine:[8,9] An initial vasoconstriction of certain intracranial branches of the internal carotid artery produces visual and possibly other preheadache phenomena before the onset of the headache. This prodromal period is followed by dilation and distention of cranial arteries, primarily in the area of distribution of the external carotid artery. Stimulation of pain-sensitive nerves in and around the dilated vessels by the increased amplitude of pulsation is the presumed cause of the headache. Persistent dilation results in a rigid, pipe-like state of the vessels. The pain at this stage is a steady ache, replacing the earlier throbbing, pulsation type. During or following this stage, there is contraction of the neck muscles, and "muscle-contraction pain" develops. This spasm of the muscles is a reaction to the initial pain and may outlast it. The initial phase of the headache is due to stimulation of pain endings which lie in or near the walls of the intracranial arteries, whereas the latter, or "muscle pain," is probably the result of either direct stimulation of nerve endings or ischemia of the muscles. Although in migraine the immediate cause of pain is associated with dilation of cranial arteries, it is evident that dilation of blood vessels alone is not sufficient to produce headache. Other dynamic or chemical factors as yet not clearly delineated must contribute.

A small but important group of patients observed by the author with the clinical features of frequent migraine headaches turned out to be schizophrenic. These patients had many pseudoneurotic symptoms which were associated with a feeling of catastrophe, oddities of behavior, a gradual withdrawal from reality and descriptions of situations which are nebulous and changeable. Such persons seldom respond to psychotherapy or medication for symptomatic treatment of an attack. The obvious schizophrenic behavior usually occurs much later. In many of these patients the nature of the mechanism is not peripheral and remains obscure. Recognition of this problem is important to avoid needless routine therapy for the patient and frustration for the physician, and to insure adequate early treatment of the schizophrenia.

4. HEADACHES ASSOCIATED WITH HYPERTENSION:

(a) *Clinical features.* The headache of arterial hypertension is usually a dull, throbbing, deep ache. It is aggravated by strain, stooping and emotional tension. This headache may be generalized or confined to the front or back of the head. Although usually bilateral, it may resemble migraine by periodicity and by being confined to one side of the head. It often appears upon the awakening of the patient and may improve as he moves about. Nausea and vomiting are infrequently noted. Another variety of headache occurring with hypertension is a suboccipital tightness and rigidity which may encircle the head.

(b) *Physiological mechanisms.* The pathogenesis of headache in essential hypertension is obscure. The degree of headache is not proportional to increased blood pressure. The headache may be present when the blood pressure is low as well as high. It is postulated that variation in the contractile state of the cranial arteries is the cause of the headache, and that the elevated blood pressure is only an accessory factor. Experimental administration of ergotamine tartrate usually abolishes the headache, which would indicate that the mechanism of pain production may be similar to that in migraine. Headache of this kind is not due to increased intracranial pressure since this pressure is normal, nor will elevating the pressure experimentally produce the pain. There is no relationship to impairment of renal function in headaches associated with hypertension. When the blood pressure is lowered by therapeutic measures, such as sodium restriction or antipressor drugs, the headache disappears.

EVALUATION OF AGENTS USED IN TREATMENT

In the past ten years the author has evaluated a number of agents in the treatment of headache. Following is a discussion of the results of three separate studies:

1. The effectiveness of drug therapy in the treatment of tension and post-traumatic headache is influenced by many factors. In a series of over five hundred patients the effectiveness of the medication depended to some extent on the physician prescribing the medication, the time he spent with the patient, and the frequency with which the patient was seen by him.[5] It was noted that in many cases patients would maintain a state of improvement if they were seen at weekly intervals, but would have recurrence of headaches if they were seen at monthly intervals instead.

In addition, the factors of disability compensation and litigation played a part in many cases of post-traumatic headache.

Fifty to sixty per cent of the patients with psychogenic and post-traumatic headache responded favorably to almost any medication given to them. The drugs used included analgesics, vasoconstrictors, vasodilators, hormones combined with vitamins, placebos, and parenterally administered isotonic sodium chloride solution. The analgesics, and some of the oral placebos were taken only at the time of the headache, while the hormone-vitamin combinations and isotonic sodium chloride solutions were given by injection at regular intervals. The effect of medication given by injection in cases of psychogenic illness is too well known to require further discussion here. In addition, several of the patients receiving the combinations of hormones and vitamins reported a feeling of well-being that undoubtedly played some part in their improvement. The similarity of response of pain with the various medications in tension and post-traumatic headache again emphasizes the close relationship between these two types of headache.

The best results in each group of patients were obtained by the use of analgesics. The other drugs gave no better results than those obtained by the use of inactive substances.

2. In a study with 2,000 patients with migraine or tension headache the following results were noted.[6] The most effective symptomatic treatment of migraine was oral or rectal administration of ergotamine tartrate and caffeine (Cafergot®). Rectal use of Cafergot proved empirically to be most efficacious especially when oral medication could not be retained. It is likely that rectal medication has the advantage of being absorbed more directly into the systemic circulation without having to penetrate the hepatic and gastric barriers. Hence it is postulated that this action is quicker with less side effects than with oral administration. This requires further investigation. The psychological connotation of taking medication via rectum must also be given consideration. Fifty-six agents were tested in this study and approximately 80 per cent of the patients received symptomatic relief by early and adequate administration of some form of ergotamine and caffeine whereas only 25 per cent had the same response to placebos. In cases of tension headache, the treatment of choice was a combination of an analgesic and sedative. Fifty different combinations of drugs were used in this study. Sixty-five per cent of the patients studied received relief symptomatically by use of analgesic-sedative combination. The placebo response in this group was close to 50 per cent.

This study indicated that, except in a few isolated cases, there are no known drugs available which are helpful prophylactically in the treatment of migraine. In an occasional case, the allergic, hormonal or metabolic factor, when adequately controlled, may prevent the onset of an attack of migraine. However, in a great majority of patients who have migraine, control of the psychic and stress factors is the most successful method of treatment.

As in migraine, there is no good prolonged medical treatment for tension headaches, although the use of sedation and some of the newer medicaments, such as Reserpine and chlorpromazine, may prove mildly successful. In general, both of these conditions require psychotherapy for adequate control, as this is the only method in which the patient's emotional conflicts can be resolved.

3. In a recent study[7] in which rauwolfia was used in a series of 220 patients with headaches that were diagnostically divided into migraine, tension and headaches associated with hypertension, it was found that in patients with migraine, 38 per cent had a reduction in frequency of these headaches; in patients with tension headaches, 75 per cent had improvement in headache status; and in patients with headache associated with hypertension, 80 per cent showed reduction in frequency of headache. However, all these data must be considered in the light of placebo experience in the same series, which indicated a favorable result in over one-half of the migraine and tension cases, and two-thirds of the cases of headache associated with hypertension.

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